REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 23, 25, 31, 33, 39 and 40 are pending in this application, of which claims 25, 33, and 40 are allowed. Claim 23 is amended. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the application. Upon entry of the amendments, claims 23, 25, 31, 33, 39 and 40 will be pending, of which claims 23, 31, and 39 will be under active consideration.

b. Amendment to the Claims

Claim 23 is amended to relate to 21-, 23-, and 24-mer miRNAs that result from Dicer enzyme processing of the hairpin having SEQ ID NO: 4233864, and are 3'-end length variants of the 22-mer miRNA with SEQ ID NO: 348 that is a result of Dicer processing of the same hairpin. As a reference, Applicant notes that SEQ ID NO: 348 corresponds to nucleotides 14-35 of SEQ ID NO: 4233864. Support for this amendment is found at the original sequence listing, and paragraphs 0050 and 0286 of the original specification. Claim 23 is also amended to clarify that each nucleotide that can be selected from the group of listed sequences must consist of the sequence described, and cannot be only a part of one of the listed sequences.

c. Interview Summary

The undersigned would like to thank the Examiner for the courtesy of conducting the in-person interview on July 29, 2010, at which the written description was discussed.

2. Patentability Remarks

a. 35 U.S.C. §112, First Paragraph, Written Description

On pages 2-4 of the Office Action, the Examiner rejects claims 23, 31, and 39 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description. The Examiner asserts that the instant application does not provide adequate written description for the isolated nucleic acids of claim 23, parts (b)-(f). In particular, the Examiner's position is that the instant application does not provide sufficient written description for 21, 23, and 24 nucleotide-long variants of instant SEQ ID NO: 348. In view of Applicant's amendment to claim 21 so that it relates to 21-, 23-, and 24-mer miRNAs that result from Dicer enzyme processing of the hairpin having SEQ ID NO: 4233864, and what was known at the time of filing the application about

miRNAs produced by Dicer processing, Applicant respectfully submits that the instant claims have adequate written description support.

There is no dispute that the instant application describes the claimed miRNA having SEQ ID NO: 348,[1] as well as the hairpin having SEQ ID NO: 4233864 from which the claimed miRNA is derived.[2] The specific question at issue is whether the specification provides sufficient written description support for variants of the claimed miRNA that are truncated by one nucleotide, or elongated by one or two nucleotides. This question must be answered not only by looking to the instant application, but also what was known about miRNAs to those skilled in the art at the time of filing.[3]

Not only does the instant application disclose the hairpin-derived miRNA having SEQ ID NO: 348, but also that hairpins processed by the Dicer enzyme complex yield an oligonucleotide that is about 19 to about 24 nucleotides in length.[4] This could be interpreted in two ways. One is that while any given miRNA has a fixed length, miRNA lengths vary between 19 and 24 nucleotides. The other is that any given hairpin is processed by the Dicer complex to produce a population of miRNAs while miRNAs that vary in length between about 19 to 24 nucleotides as a consequence of hairpin processing. Under this interpretation, the explicit description of a particular miRNA sequence that is 22 nucleotides in length **necessarily** establishes possession of Dicer-processed variants that are truncated or elongated. Applicant submits that based on the specification and what was known at the time of filing about hairpin processing by the Dicer complex, this latter interpretation is correct.

The miRNA maturation process was understood at the time of filing.[5] The process begins with transcription of a hairpin (a "Pri-miRNA") from a miRNA gene. The hairpin is processed by the Drosha enzyme into a shorter hairpin structure, and subsequently processed by the Dicer enzyme complex into a miRNA/miRNA* complex.[6] Dicer was known to process miRNA

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[1] *See* Instant claim 23 part (a).

[2] *See* Instant allowed claim 25.

[3] *See* MPEP § 2163.II.A.2 ("[A] review [of compliance with the written description requirement] is conducted from the standpoint of one of skill in the art at the time the application was filed [citation omitted] and should include a determination of the field of the invention and the level of skill and knowledge in the art").

[4] Instant Specification at paragraph 0050 ("A 'Hairpin-Shaped Precursor' is defined as a Hairpin Structure which is processed by a Dicer enzyme complex, yielding an oligonucleotide which is about 19 to about 24 nts in length").

[5] *See* Bartel, D.P., "MicroRNAs: Genomics, Biogenesis, Mechanism, and Function," Cell, 2004;116:281-97.

[6] *See* Bartel at Figure 2B.

precursors through a mechanism similar to dsRNAs.[7] It was further known that Dicer does not yield an oligonucleotide that has a fixed length from a given precursor, but rather that Dicer produces oligonucleotides that vary in length between 18-24 nucleotides, and typically between 21-23 nucleotides in length.[8] Many cloned miRNAs were known to exhibit this kind of length variation at the 3' end.[9] For example, Lim discloses miRNA length ranges of 21-24 (miR-228), 19-23 (miR-233), and 21-25 nucleotides (miR-236), and describes that the length heterogeneity occurs at the 3' terminus

Turning to the instant application, the specification discloses that any given miRNA can vary in length, and that the variation occurs at the 3' end. In particular, the specification describes experiments that were performed by Applicant to validate the existence of miRNAs predicted using bioinformatics methods.[10] Applicant accomplished the validation by using a PCR-based approach that relied on a primer that was hemi-specific for an adaptor that had been ligated to the end of an isolated miRNA, as well as hemi-specific for the 5' end of the miRNA.[11] By virtue of this design, the validation experiments were specifically capable of detecting variability at the 3' end of the miRNA.

Applicant submits that this design is consistent with the understanding at the time of filing by those of skill in the art that the 3' ends of miRNAs exhibited length variability as a result of hairpin processing by Dicer. The instant specification specifically acknowledges this understanding in describing the validation experiments when it discloses how, "[t]he 3' terminus of observed GAM RNA [miRNA] sequences is often truncated or extended by one or two nucleotides."[12] One of ordinary skill in the art would thus reasonably conclude that Applicant was in possession of not only

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[7] *See* Bartel at page 285, column 2, paragraph 2 ("…Dicer performs an activity in metazoan miRNA maturation similar to that which it performs in chopping up double-stranded RNA during RNAi…").

[8] *See* Zamore, P.D., *et al.*, "RNAi: Double-Stranded RNA Directs the ATP-Dependent Cleavage of mRNA at 21 to 23 Nucleotide Intervals," Cell, 2000;101:25-33 at Figure 3 (showing a gel of oligonucleotides produced by Dicer processing of a precursor, where the gel clearly shows oligonucleotide products of 21, 22, and 23 nucleotides in length) *and see* Elbashir, S.M. *et al.*, "RNA interference is mediated by 21- and 22-nucleotide RNAs", Genes and Development, 2001;15:188-200 at page 190, column 2, paragraph 4 (describing how a dsRNA precursors yielded dsRNA products that varied in length from 18 to 24 nucleotides).

[9] *See* Lim, L.P. *et al.*, "The microRNAs of *Caenorhabditis elegans*," Genes & Dev., 2003;17:991-1008 ("Lim" hereafter) at Table 2 *and see also* Morin, R.D. *et al.*, "Application of massively parallel sequencing to microRNA profiling and discovery of human embryonic stem cells," Genome Res., 2008;18:610-21 at Figure 2 and Supplemental Table 4 (showing a number of miRNA that have a length range of at least 20-24 nucleotides, where the length variation occurs at the 3' end).

[10] *See* Instant Application at paragraphs 0279-0314.

[11] Instant Applicant at paragraph 0282.

[12] Instant Specification at paragraph 0284.

the miRNA having SEQ ID NO: 348, but also miRNAs that vary from it in length at the 3' end, and in particular variants that are truncated by one nucleotide, and elongated by one or two nucleotides. Accordingly, Applicant submits that the subject matter of claims 23, 31, and 39 has adequate written description support, because the specification need only convey possession of claimed subject matter with reasonable clarity in order to satisfy the written description requirement.[13] Applicant further submits that the Examiner must present "by a **preponderance of evidence** why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims,"[14] and that the Examiner cannot meet this burden in view of the record as a whole.[15] In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 23, 31, and 39 under 35 U.S.C. § 112, first paragraph.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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[13] *See* MPEP § 2163.02 ("[T]he fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed").

[14] MPEP § 2163.04 (emphasis added).

[15] *See* MPEP § 2163.04.II ("Upon reply by applicant, before repeating any rejection under 35 U.S.C. 112, para. 1, for lack of written description, review the basis for the rejection in view of the record as a whole…").